

Rice, A., Michaelis, M.L., Georg, G., Liu, Y., Turunen, B., and Audus, K.L. (2003) Overcoming the blood-brain barrier to taxane delivery for brain tumors and neurodegenerative diseases and brain tumors. J. Mol. Neurosci. 20, 339-344. PMID: 14501017. Publisher's official version: <<http://dx.doi.org/10.1385/JMN:20:3:339>> . Open Access version: <http://kuscholarworks.ku.edu/dspace/>.

[This document contains the author's accepted manuscript. For the publisher's version, see the link in the header of this document.]

Paper citation: Rice, A., Michaelis, M.L., Georg, G., Liu, Y., Turunen, B., and Audus, K.L. (2003) Overcoming the blood-brain barrier to taxane delivery for brain tumors and neurodegenerative diseases and brain tumors. J. Mol. Neurosci. 20, 339-344. PMID: 14501017

Keywords: Blood brain barrier; CNS drug permeation; microtubule-stabilizing drugs; taxol; brain microcapillary endothelial cells; neurofibrillary pathology.

Abstract: The blood-brain barrier (BBB) effectively prevents microtubule stabilizing drugs from readily entering the central nervous system (CNS). A major limiting factor for microtubule stabilizing drug permeation across the BBB is the active efflux back into the circulation by the over-expression of the multidrug resistant gene product (MDR1) or P-glycoprotein (P-gp). This study has focused on strategies to overcome P-gp-mediated efflux of taxol analogues, microtubule (MT) stabilizing agents that could be used to treat brain tumors and, potentially, neurodegenerative diseases such as Alzheimer's disease. However, taxol is a strong P-gp substrate which limits its distribution across the BBB and therapeutic potential in the CNS. We have found that addition of a succinate group to the C-10 position of taxol results in an agent, Tx-67, with reduced interactions with P-gp and enhanced permeation across the BBB in both *in vitro* and *in situ* models. Our studies demonstrate the feasibility of making small chemical modifications to taxol to generate analogues with reduced affinity for the P-gp but retention of MT-stabilizing properties, i.e., a taxane that may reach and treat therapeutic targets in the CNS.

Text of paper:

OVERCOMING THE BLOOD-BRAIN BARRIER TO TAXANE DELIVERY FOR NEURODEGENERATIVE DISEASES AND BRAIN TUMORS

Antonie Rice¹, Mary L. Michaelis², Gunda Georg³, Yanbin Liu³,

Brandon Turunen³, Kenneth L. Audus¹

**¹Department of Pharmaceutical Chemistry
University of Kansas, 226 Simons**

2095 Constant Avenue

Lawrence, KS 66047

²Department of Pharmacology and Toxicology

University of Kansas, Malott Hall 5064

1251 Wescoe Hall Drive

Lawrence, KS 66045

³Department of Medicinal Chemistry

Univerisity of Kansas, Malott Hall 4070

1251 Wescoe Hall Drive

Lawrence, KS 66045

Introduction

The delivery of therapeutic agents into the brain continues to be a challenge for the pharmaceutical industry. Due to the inadequate delivery of these agents to the desired site of action in the brain, many neurological disorders (i.e., brain tumors, Alzheimer's disease, and other brain disorders) have poor responses to drug treatment (Pardridge, 2002). We have previously shown in neuronal cell cultures that the microtubule-stabilizing drug taxol protects neurons against amyloid peptide (A β) toxicity (Michaelis et al., 1998, 2002). The potential for testing protective effects *in vivo* is severely limited by the failure of taxol and several of its derivatives to enter the brain. Consequently, we have synthesized a large array of MT-stabilizing drugs related to taxol and tested them for potential to penetrate into the brain. In this paper we discuss the strategies we have tested and the results obtained regarding brain permeability of one promising taxane.

The blood-brain barrier (BBB) regulates the influx and efflux of a wide variety of substances and remains the major obstacle in the delivery of drugs into the central nervous system (CNS). The most common mechanism for drug distribution across the BBB is by simple passive diffusion; however, once a drug enters the endothelial lining of the BBB by this mechanism, it may either undergo passive diffusion or active transport back out of the cells into the circulation. First identified in tumors, the active efflux transport mechanisms are implicated as major factors in limiting the effective delivery of a number of drugs and drug classes across the BBB (Schinkel, 1999; Taylor, 2002). The transporters responsible for the active efflux of drugs at the BBB include the multidrug resistant gene product 1 (MDR1) or P-glycoprotein (P-

gp), multidrug resistance-associated proteins (MRPs), and the breast cancer resistance protein (BCRP). The major efflux pump at the BBB is MDR or P-glycoprotein (Schinkel, 1999; Taylor, 2002).

P-glycoprotein is a member of the ATP-binding cassette (ABC) family of transport proteins (Gottesman et al., 1996). This transporter is located on the blood side of the capillary endothelial cell and is involved in the efflux of a wide range of substrates that include antineoplastic agents (e.g., vincristine, vinblastine, and taxol), antiviral compounds (e.g., saquinavir, ritonavir, indinavir), opiates, and other therapeutic agents. Various strategies have been devised to circumvent the BBB in order to increase drug delivery to the CNS. These strategies involve attempts to manipulate either the chemical properties of the agent, opening the BBB by increasing capillary endothelial permeability, or enhancing the driving force for transport by increasing the plasma concentration of a drug (i.e., high dose chemotherapy, intra-arterial injection) (Taylor, 2002; Siegal and Zylber-Katz, 2002).

The strategy we chose to overcome the BBB efflux mechanisms was to focus on the use of combinatorial chemistry to manipulate chemical structure in order to reduce affinity for P-gp. This type of approach has been successfully used, for example, to generate molecular diversity in chemical structures for the development of new antibacterial agents in order to overcome bacterial-drug resistance (Desnottes, 1996). The starting point for our work was to generate and screen newly synthesized analogues of the anticancer agent, paclitaxel or taxol, for taxanes that have reduced P-gp affinity relative to the parent drug. Taxol, one of the leading anticancer drugs currently on the market for the treatment of ovarian and breast

cancer, is very effective in treating tumors but, unfortunately, is also a substrate for the P-gp efflux pump. Due to interactions with P-gp at the BBB, it is almost impossible to infuse taxol vascularly to treat brain tumors (Cahan et al., 1994; Brouty-Boye et al., 1995; Lovich et al., 2001; Fellner et al., 2002). Therefore, second-generation taxanes that retain appropriate pharmacological activity and have reduced interactions with P-gp were generated with the primary objective of improving distribution across the BBB. To characterize these new taxanes we have employed a combination of *in vitro* and *in situ* models of the BBB. The goals of experiments described herein were to: 1) determine which newly synthesized taxanes have reduced P-gp interactions and improved permeability properties relative to taxol, using an *in vitro* model comprised of P-gp-expressing primary cultures of brain microvessel endothelial cells, and 2) determine which newly synthesized taxanes have improved permeability properties relative to taxol at the BBB, using an *in situ* rat brain perfusion model. Taxol and the taxanes that were employed in the permeability assays here have previously been shown to retain appropriate pharmacological properties with respect to protecting neurons against A β -induced toxicity (Michaelis et al., 1998; 2002).

Methods

Bovine brain microvessel endothelial cells (BBMECs) were isolated from the gray matter of cerebral cortices by enzymatic digestion and subsequent centrifugation, and seeded into primary culture as described (Audus and Borchardt, 1987; Audus et al. 1996). Uptake and transport studies were performed in pH 7.4 standard buffer solutions, consisting of either Hank's balanced salt solution (HBSS) or phosphate buffered saline (PBS) supplemented with 0.63 mM CaCl₂, 0.74 mM MgSO₄, 5.3 mM

glucose, and 0.1 mM ascorbic acid (PBSA). [³H] Taxol (specific activity 10.5 Ci/mmol) was obtained from Moravek Radiochemicals. Dr. Gunda Georg, Medicinal Chemistry Department, University of Kansas, supplied the taxol and taxane analogs. Rhodamine 123 (Rho 123) and cyclosporin A (CsA) were obtained from Sigma.

Rhodamine 123 Accumulation in the Presence of Taxanes

BBMECs were grown in 12-well plates to form confluent monolayers and used as described to assay for P-gp as detailed elsewhere (Rose et al., 1998). Briefly, the fluorescent marker Rho 123 was dissolved in PBSA buffer to give a stock concentration of 100 µM. The uptake assay was performed in 1 ml of fresh PBSA. An aliquot of taxol or one of its analogues was added to each well to give a final concentration of 25 µM. As a positive control, the P-gp inhibitor CsA (5 –10 µM) was used. The negative control was rhodamine (5-10 µM) alone. The cells were pre-incubated at 37 °C with taxol or an analogue for approximately 45 min. After this pre-incubation period, Rho 123 was added to the cells. After a 45-min incubation, the cells were washed in cold PBS and lysed in a NaOH/Triton X-100 solution. The cell lysates were assayed using a fluorescence spectrophotometer. Rho 123 was measured at excitation/emission wavelengths of 500 nm/535 nm, and quantified against a standard curve of Rho 123 in the appropriate lysing solution. The protein content was determined using the BCA protein assay reagent kit and the results were expressed as total fluorescence accumulation per mg of cell protein.

Transport of Taxanes across BBMEC Monolayers

The BBMECs were grown on 0.4 µm pore polycarbonate membranes essentially as described (Audus and Borchardt 1987; Audus et al. (1996). When they reached confluency, the cells were transferred to side-by-side diffusion chambers to characterize the transport of a small number of promising tritium-labeled by assessing their permeability relative to that of the

paracellular marker [^{14}C]-sucrose as an index of monolayer confluency. Bi-directional transport was assessed for each of the radiolabeled compounds to determine if polarized transport was observed. All of the studies were performed in 3 ml of stirred PBSA in each donor and receiver chamber at 37°C. The cells were allowed to equilibrate in PBSA for 30 minutes prior to the experiment. At each time point, 100 μl of sample were taken from the receiver compartment and immediately replaced with an equal volume of PBSA. Apparent permeability coefficients (P_{app}) were calculated according to the following equation:

$$P_{\text{app}} = (V/AC_0) * (dC/dt)$$

Where V= volume of the receiver chamber (3.0 cm^3), A = area of the filter (0.636 cm^2), C_0 = initial donor concentration and (dC/dt) = flux of the test agent.

In Situ Rat Brain Perfusion of Taxanes

The *in situ* rat brain perfusion technique described by Smith (1996), was employed to determine the BBB permeability of taxol and the taxane analog Tx-67. Adult male Sprague-Dawley rats (350-400g) were anesthetized with a mixture containing: 1.5 ml/kg of solution consisting of 37.5 mg/ml ketamine, 1.9 mg/ml xylazine, and 0.37 mg/ml acepromazine. The rat brain was then directly perfused through the left carotid artery with a buffered physiologic saline containing a tracer (sucrose) as a vascular marker and the sample ($[^3\text{H}]$ -taxol or $[^{14}\text{C}]$ -Tx-67) for time periods of 30, 60, or 120 seconds. The perfusion solution was changed to tracer-free fluid for 30 sec to clear the labeled compound from the cerebral vessels. After the perfusion, the rat was decapitated and the brain removed for sampling of various regions. The brain tissue was digested in Solvable for 24 hrs and the radioactivity quantified via liquid scintillation spectrometry. The capillary permeability-surface area product (PA) (ml/s/g) was calculated for both taxol and Tx-67 by the following equation:

$$PA = -F \ln [1 - C^*_{\text{br}}(T) / F T C^*_{\text{pf}}]$$

Where F is the regional cerebral blood flow (ml/s/g); C^*_{br} represents the concentration of tracer in the brain parenchyma (dpm/g); C^*_{pf} is the concentration in the perfusion fluid (dpm/ml); and T is the total perfusion time.

Results

Rhodamine 123 accumulation was assessed in the presence of taxol and the new analogues of taxol. Although it is an indirect assay, our studies revealed that some of the synthetic taxanes appeared to have reduced interactions with P-gp (i.e., no increase in Rho 123 accumulation in the presence of the analogues). Taxol, a known substrate for P-gp, increased rhodamine uptake by 2-2.5 fold in the BBMECs. Rhodamine uptake in the presence of taxol was very similar to that observed in the presence of the positive control, CsA (5 μ M), a known P-gp inhibitor. Accordingly, from the Rho 123 screening of numerous taxanes in multi-well dish formats, we obtained a rather quick analysis of which taxanes were poor substrates efflux by P-gp. One of the taxanes that had no apparent interactions with P-glycoprotein, i.e., no effect on Rho 123 uptake by BBMECs, was designated 'Tx-67', a compound in which a succinate group was added at the C-10 position of taxol.

We next assessed the actual permeability properties of Tx-67 relative to taxol. Given that the BBMECs have an apical and a basolateral surface when grown on polycarbonate membranes, our permeation studies included an assessment of whether the permeation was polarized or asymmetric in nature. We used radiolabeled taxol and Tx-67 for these experiments to provide sensitivity in the nM concentration range. The apparent permeability coefficient for

taxol was greater in the basolateral (b) to apical (a) direction (i.e., $b \rightarrow a > a \rightarrow b$). We also observed that the analogue, Tx-67, had enhanced permeation compared to that of taxol. The apparent permeability coefficient of Tx-67 at any concentration (low or high) was substantially greater than the P_{app} for taxol at the highest concentration used (25 μ M). Moreover, the permeation of Tx-67 was asymmetric, but greater in the apical to basolateral direction which suggests greater blood to brain permeation for the new taxane. Figure 1 shows typical results for taxol and Tx-67 permeability at 20 nM, a concentration at which the BBMEC P-gp is not saturated, and at 10 μ M, a concentration at which the transporter is presumed to be saturated and thus the permeability of the monolayers to both agents significantly increased. It is important to note that BBMEC monolayer permeability to radiolabeled sucrose (i.e., a marker for integrity and background monolayer “leakage”) was not altered by exposure to either taxol or Tx-67 under the conditions of these experiments.

In the *in situ* perfusion experiments with [14 C] Tx-67 and [3 H] taxol, we observed a substantially greater apparent permeability coefficient for Tx-67 relative to taxol. It appears that the taxol is not retained in the rat brain tissue as only minimal amounts (2.5% or less of total control) were detectable in the brain at 120 sec. Approximately 6 to 8% of the total Tx-67 was detectable after 60 sec of perfusion. Table 1 lists the P_{app} s determined for Tx-67 and taxol at each perfusion time.

Table 1. The Apparent Permeability Coefficients for [14 C] Tx-67 and [3 H] Taxol in the *in situ* rat brain perfusion. Time points were for: 30, 60, and 120 seconds (each time point was determined in duplicate experiments).

$P_{app} \times 10^7$ cm/sec

Compound	30 sec	60 sec	120 sec
[¹⁴ C] Tx-67	8.47	13.71	10.75
[³ H] Taxol	0.845	1.700	1.574

Discussion

The initial Rho 123 screening of newly synthesized taxanes showed that some structural modifications to taxol generated through combinatorial chemistry approaches lead to compounds that appear to be less avid substrates for P-gp than the parent taxol. Clearly taxol competes with Rho 123 for P-gp, resulting in increased fluorescence using this screening technique. On the other hand, Tx-67 appeared to interact with P-gp to a significantly lesser degree in the same assay. Despite the addition of the succinyl group, Tx-67 retained its MT-stabilizing properties and its effectiveness in protecting neurons against A β -induced toxicity as reported earlier (Michaelis et al., 2002). These findings are consistent with studies in other laboratories that show second-generation taxanes have reduced interactions with P-gp and yet still exhibit potent anticancer activity (Ojima et al., 1996; Ojima and Slater, 1997).

We also determined that the transport of taxol across BBMEC monolayers was asymmetric and supports previous data that the P-gp is localized on the apical side of the brain (Cordon-Cardo et al., 1989; Tsuji et al., 1992). However, the new taxane, Tx-67, although asymmetric in permeation across the monolayers, showed a much higher permeability favoring what would be blood to brain distribution in this model. The *in situ* rat brain perfusion data correlated well with our *in vitro* permeability data, showing that Tx-67 permeation across the BBB was in fact substantially greater than the permeation of

Taxol into rat brains. Our taxol data were comparable to perfusion data for other anticancer drugs such as vincristine and vinblastine (Greig et al., 1990).

We have demonstrated that the use of combinatorial chemistry led to synthesis of new taxanes with reduced interactions with P-glycoprotein. We have also been able to demonstrate that one of the newly synthesized analogs, Tx-67, appears to cross the BBB both *in vitro* and *in situ* more readily than the parent drug. The Tx-67 permeation studies support our hypothesis that chemical modification of taxol does enhance its permeability into the brain. In addition, the work is consistent with literature observations where small changes in chemical structures can alter interactions with P-glycoprotein at the BBB and thereby influence the distribution of the agents into the CNS (Mann et al., 1997). The most significant aspect of these results is that we now have an agent with MT-stabilizing activity and strong neuroprotective actions against A β in primary neuronal cultures that can be tested *in vivo*. Studies are being undertaken to characterize the pharmacokinetic and pharmacodynamic properties of Tx-67 in mice. This is being done in anticipation of testing its therapeutic potential in animal models of both neurodegenerative diseases and brain tumors.

Acknowledgements

This work was supported by the Institute for the Study of Aging, Inc., New York and an NIH grant (NCI 1 RO1 CA82801).

References

Audus K.L. and Borchardt R.T. (1987) Bovine brain microvessel endothelial cell monolayers as a model system for the blood-brain barrier. *Ann. N.Y. Acad. Sci.* **507**, 9-18.

Rice, A., Michaelis, M.L., Georg, G., Liu, Y., Turunen, B., and Audus, K.L. (2003) Overcoming the blood-brain barrier to taxane delivery for brain tumors and neurodegenerative diseases and brain tumors. *J. Mol. Neurosci.* 20, 339-344. PMID: 14501017. Publisher's official version: <<http://dx.doi.org/10.1385/JMN:20:3:339>> . Open Access version: <http://kuscholarworks.ku.edu/dspace/>.

Audus K.L., Ng L., Wang W., and Borchardt R.T. (1996) Brain microvessel endothelial cell culture systems. *Pharm. Biotechnol.* **8**, 239-258, 1996

Brouty-Boye, D., Kolonias, D., Wu, C. J., Savaraj, N., and Lampidis, T. J. (1995). Relationship of multidrug resistance to rhodamine-123 selectivity between carcinoma and normal epithelial cells: taxol and vinblastine modulate drug efflux. *Cancer Res.* **55**, 1633-1638.

Cahan, M. A., Walter, K. A., Colvin, O. M., and Brem, H. (1994). Cytotoxicity of taxol in vitro against human and rat malignant brain tumors. *Cancer Chemother.Pharmacol.* **33**, 441-444.

Cordon-Cardo, C., O'Brien, J. P., Casals, D., Rittman-Grauer, L., Biedler, J. L., Melamed, M. R., and Bertino, J. R. (1989). Multidrug-resistance gene (P-glycoprotein) is expressed by endothelial cells at blood-brain barrier sites. *Proc.Natl.Acad.Sci.U.S.A* **86**, 695-698.

Desnottes, J. F. (1996). New targets and strategies for the development of antibacterial agents. *Trends Biotechnol.* **14**, 134-140.

Rice, A., Michaelis, M.L., Georg, G., Liu, Y., Turunen, B., and Audus, K.L. (2003) Overcoming the blood-brain barrier to taxane delivery for brain tumors and neurodegenerative diseases and brain tumors. *J. Mol. Neurosci.* 20, 339-344. PMID: 14501017. Publisher's official version: <<http://dx.doi.org/10.1385/JMN:20:3:339>> . Open Access version: <http://kuscholarworks.ku.edu/dspace/>.

Fellner S., Bauer B., Miller D.S., Schaffrik M., Franhanel M., Spruss T., Bernhardt G., Graeff C., Farber L., Gschaidmeier H., Buschauer A., and Fricker G. (2002) Transport of paclitaxel (Taxol) across the blood-brain barrier in vitro and in vivo. *J. Clin. Invest.* **110**, 1309-1318.

Gottesman, M. M., Pastan, I., and Ambudkar, S. V. (1996). P-glycoprotein and multidrug resistance. *Curr.Opin.Genet.Dev.* **6**, 610-617.

Greig, N. H., Soncrant, T. T., Shetty, H. U., Momma, S., Smith, Q. R., and Rapoport, S. I. (1990). Brain uptake and anticancer activities of vincristine and vinblastine are restricted by their low cerebrovascular permeability and binding to plasma constituents in rat. *Cancer Chemother.Pharmacol.* **26**, 263-268.

Lovich, M. A., Creel, C., Hong, K., Hwang, C. W., and Edelman, E. R. (2001). Carrier proteins determine local pharmacokinetics and arterial distribution of paclitaxel. *J.Pharm.Sci.* **90** , 1324-1335.

Mann H., Ladenheim B., Hirata H., Moran T.H., and Cadet J.L. (1997) Differential toxic effects of methamphetamine (METH) and methylenedioxymethamphetamine (MDMA) in multidrug resistant (mdr1a) knockout mice. *Brain Res.* **769**, 340-346.

Rice, A., Michaelis, M.L., Georg, G., Liu, Y., Turunen, B., and Audus, K.L. (2003) Overcoming the blood-brain barrier to taxane delivery for brain tumors and neurodegenerative diseases and brain tumors. *J. Mol. Neurosci.* 20, 339-344. PMID: 14501017. Publisher's official version: <<http://dx.doi.org/10.1385/JMN:20:3:339>> . Open Access version: <http://kuscholarworks.ku.edu/dspace/>.

Michaelis ML, Ranciat N., Chen Y., Bechtel M., Ragan R., Hepperle M., Liu Y., and Georg G. (1998)

Protection against β -amyloid toxicity in primary neurons by paclitaxel (Taxol). *J. Neurochem.* **70**, 1623-1627.

Michaelis M.L., Chen Y., Hill S., Reiff E., Georg G., Rice A., and Audus K.L. (2002) Amyloid peptide toxicity and microtubule-stabilizing drugs. *J. Mol. Neurosci.* **19**, 101-105.

Ojima I. and Slater J. C. (1997) Synthesis of novel 3'-trifluoromethyl taxoids through effective kinetic resolution of racemic 4-CF₃-beta-lactams with baccatins. *Chirality* **9**, 487-494.

Ojima I., Slater J. C., Michaud E., Kuduk S. D., Bounaud P. Y., Vrignaud P., Bissery M. C., Veith J. M., Pera P., and Bernacki R. J. (1996). Syntheses and structure-activity relationships of the second-generation antitumor taxoids: exceptional activity against drug-resistant cancer cells. *J. Med. Chem.* **39**, 3889-3896.

Pardridge W.M. (2002) Targeting neurotherapeutic agents through the blood-brain barrier. *Arch. Neurol.* **59**, 35-40.

Rice, A., Michaelis, M.L., Georg, G., Liu, Y., Turunen, B., and Audus, K.L. (2003) Overcoming the blood-brain barrier to taxane delivery for brain tumors and neurodegenerative diseases and brain tumors. *J. Mol. Neurosci.* 20, 339-344. PMID: 14501017. Publisher's official version: <<http://dx.doi.org/10.1385/JMN:20:3:339>> . Open Access version: <http://kuscholarworks.ku.edu/dspace/>.

Rose J.M., Peckham S.L., Scism J.L., and Audus K.L. (1998) Evaluation of the role of P-glycoprotein in ivermectin uptake by primary cultures of bovine brain microvessel endothelial cells. *Neurochem. Res.* **23**, 203-209.

Schinkel, A. H. (1999). P-Glycoprotein, a gatekeeper in the blood-brain barrier. *Adv. Drug Deliv. Rev.* **36** , 179-194.

Siegal, T. and Zylber-Katz, E. (2002). Strategies for increasing drug delivery to the brain: focus on brain lymphoma. *Clin Pharmacokinet.* **41**, 171-186.

Smith Q. (1996) Brain perfusion systems for studies of drug uptake and metabolism in the central nervous system. *Pharm. Biotechnol.* **8**, 285-307.

Taylor, E. M. (2002). The Impact of Efflux Transporters in the Brain on the Development of Drugs for CNS disorders. *Clin Pharmacokinetics* **41**, 81-92.

Tsuji, A., Terasaki, T., Takabatake, Y., Tenda, Y., Tamai, I., Yamashima, T., Moritani, S., Tsuruo, T., and Yamashita, J. (1992). P-glycoprotein as the drug efflux pump in primary cultured bovine brain capillary endothelial cells. *Life Sci.* **51**, 1427-1437.

Rice, A., Michaelis, M.L., Georg, G., Liu, Y., Turunen, B., and Audus, K.L. (2003) Overcoming the blood-brain barrier to taxane delivery for brain tumors and neurodegenerative diseases and brain tumors. *J. Mol. Neurosci.* 20, 339-344. PMID: 14501017. Publisher's official version: <<http://dx.doi.org/10.1385/JMN:20:3:339>> . Open Access version: <http://kuscholarworks.ku.edu/dspace/>.

Figure Legends:

Figure 1. Concentration-dependence of apparent permeability coefficients (Papp) for taxol and Tx-67 permeation across primary cultures of BBMEC monolayers at 37°C. The data summarized are the Papps for taxane permeation from the apical (blood) to basolateral (brain) side of the monolayers. The data points are means \pm standard deviations for at least four different monolayers.

Rice et al.

Figure 1

